REMARKS

Upon entry of the foregoing amendment, claims 24-51 are pending in the application. Applicants respectfully request reconsideration of the outstanding objections and rejection set forth in the Office Action in view of the following Remarks.

Amendments to the Specification

Applicants have amended the specification to insert the priority claim. Applicants respectfully submit that the priority claim was contained in the Application Data sheet filed on June 23, 2004. Accordingly, no petition or fee is required for entry of this amendment. See Manual for Patent Examining Procedure ("M.P.E.P.") at § 201.11III(D). No new matter is added as a result of these amendments.

Applicants have also amended the specification to correct an error in translation. In the translation of PCT/JP03/04590 from Japanese to English, certain Japanese characters were inadvertently and mistakenly translated into the word "and" in U.S. Patent Application 10/500,0018 as filed. See Declaration of Yasuhiko Kinomura. It is the object of this declaration to correct the translation error with respect to these Japanese characters which mean "or" not "and." See Id. Support for these changes may be found in PCT/JP03/04590 and JP 109761/2002. No new matter is added as a result of these amendments.

Applicants respectfully request entry of the above amendments to the specification.

Claim Amendments

Claims 24, 25, 30, 35, 36, 41, and 43-46 have been amended. Support for the amendments to the claims can be found throughout the specification and in the claims as originally filed. No new matter is added as a result of these amendments.

Applicants have also amended claims 35 and 41 to correct an error in translation. As discussed above, in the translation of PCT/JP03/04590 from Japanese to English, certain Japanese characters were inadvertently and mistakenly translated into the word "and" in U.S. Patent Application 10/500,0018 as filed. See Declaration of Yasuhiko Kinomura. It is the object of this declaration to correct the translation error with respect to these Japanese characters which mean "or" not "and." See Id. Support for these changes may be found in PCT/JP03/04590, JP

109761/2002, and throughout the specification and in the claims as originally filed. No new matter is added as a result of these amendments.

Applicants respectfully request entry of the above amendments to the claims.

Objections to the Specification

The specification was objected to because the priority data needed to be updated on page 1.

Applicants have amended the specification to insert the priority data rendering this objection *moot*.

Reconsideration and withdrawal of the objection is respectfully requested.

Objections to the Claims

Claims 25-26, 31-33, 37, 39-40, 44, 46-49, and 51 were objected to as being dependent upon a rejected base claim.

Applicants respectfully request that this objection be held in abeyance until allowable subject matter is reached at which time, Applicants will address this objection.

Enablement Rejection under 35 U.S.C. § 112 ¶ 1

Claims 24, 27-30, 34-36, 38, 41-43, 45, and 50 stand rejected under 35 U.S.C. § 112, ¶ 1, on the grounds that the specification, while being enabled for *methods of producing a protected ghrelin peptide fragment and methods for producing a modified peptide by using an OmpT protease and Kex2 protease*, allegedly does not reasonably provide enablement for *methods of producing protected ghrelin peptide fragment derivatives or methods for producing a modified peptide using derivatives of OmpT protease and Kex2 protease having functional cleavage function*. Applicants respectfully disagree and traverse this rejection.

In order to meet the legal standard for establishing an enablement rejection, the Office Action must establish a *prima facie* case that undue experimentation is required to make and use the instantly claimed invention. M.P.E.P. § 2164.01. In In re Wright, the Federal Circuit held that, "[w]hen rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention

provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." 999 F.2d 1557, 1561-62, 27 U.S.P.Q.2d 1510 (Fed. Cir. 1993). Accordingly, a proper enablement rejection requires evidence to establish that the claimed invention would require undue experimentation. See also In re Bowen, 492 F.2d 859, 862-63, 181 U.S.P.Q. 48, 51 (CCPA 1974).

Applicants respectfully submit that the Office Action has not meet this standard. As an initial matter, Applicants respectfully submit that the Office Action improperly limits the invention to a method of producing only ghrelin, OmpT protease and Kex2 protease peptides and proteins. In contrast, independent claims 24 and 41 are directed to methods for producing protected peptide fragments containing modified amino acids or non-amino acids and methods for producing protected peptide fragments containing no modified amino acids or non-amino acids, respectively. The method for producing peptide fragments containing a modified site is carried out using a chemical synthesis method, whereas the method for producing peptide fragments uses a genetic modification method. See Specification at 11.

The specification clearly sets out steps for carrying out the peptide synthesis comprising a method in which a peptide main chain sequence of a peptide fragment is constructed on a weak acid-cleavable resin. The peptide is selectively modified and treated with a weak acid. Then a protected and modified peptide can be cleaved from the solid phase resin. See Specification at 12. Furthermore, claim 21 is drawn to a method of producing a protected peptide fragment comprising four steps: (1) preparing a peptide main chain sequence of a peptide fragment on weak acid-cleavable resin and protecting one or more reactive functional groups in a side chain of the peptide; (2) deprotecting the protected side group without cleaving from the weak acid-cleavable resin; (3) modifying the side chain with a substituent R; and (4) cleaving the peptide fragment from the weak acid-cleavable resin under weakly acidic conditions. Applicants respectfully submit that no undue experimentation is required to carry out the instantly claimed method. See also In re Wands, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

Therefore, the instant invention relates to a solid-phase peptide synthesis method applicable to a desired peptide and the specification provides ample guidance for performing this method at pages 15-26. Further, Ghrelin, OmpT protease, and Kex2 protease are only non-limiting examples provided in the specification to illustrate products made by the claimed

method and not specific claim limitations in the independent claims. See Examples 10-15 of the specification.

The Office Action asserts that, "practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art to ascertain which derivatives of ghrelin peptide, OmpT protease, and Kex2 protease function in the same way as the wild-type protein." See Office Action at 3. The Office Action further states that, "[n]o working examples are present of derivative ghrelin peptide fragment derivatives, OmpT protease, and Kex2 protease proteins." See Office Action at 4. Applicants respectfully disagree.

Applicants respectfully submit that the specification provides sufficient disclosure for the enablement of methods for producing a protected peptides such as derivatives of ghrelin, OmpT protease and Kex2 protease but the Office Action does states that, "[t]he relative level of skill in this art is very high." Office Action at 5. It is well-established in patent law that the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. In re Buchner, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991). Here, the specification teaches that chemical synthesis methods for producing peptides are known but there is room for improvement in yield, purity, and the cost. Specification at 4 lines 4-26; 6 lines 13-18.

Regarding ghrelin derivatives, Applicants respectfully submit that ghrelin derivatives are known in the art and, for example are specifically disclosed in EP 1 197 496 A1 (attached herein as **Exhibit 1**). In addition, EP 1 197 496 A1 not only describes the activity of increasing the calcium ion concentration in a cell shown by ghrelin derivatives, but also teaches an assay methods such as the Ca^{2+}-releasing activity, the effect on the secretion of pituitary hormones, and the increase of cardiac output in a rat by ghrelin and ghrelin derivatives. Id. at Examples 4, 6-7; Tables 4-7. EP 1 197 496 A1 also teaches structural comparison and synthesis of ghrelin and several ghrelin derivatives. Id. at Examples 9-10; Table 3. Under these circumstances, the skilled artisan could easily refer to EP 1 197 496 A1, to find the chemical structures of active ghrelin derivatives which could be produced by the method of the present invention, as well as assays to test activity their activity.

Regarding Kex2 protease derivatives, Applicants respectfully submit that Kex2 protease derivatives are disclosed in U.S. Patent No. 5,162,220 (attached herein as **Exhibit 2**) and U.S. 5,885,821 (attached herein as **Exhibit 3**). U.S. Patent No. 5,162,220 teaches the structure,

activity, and production of Kex2 derivatives. Id. at Tables 1-3; Examples 4 & 6. U.S. 5,885,821 teaches the structure (including sequences), activity, and production of Kex2 derivatives. Id. at Figure 25; Examples 2-10. In view of these references, the skilled artisan has sufficient guidance to prepare Kex2 protease derivatives which are applicable in the present invention being provided with the structure (sequence), function (assays), and methods of production (recombinant) of Kex2 protease derivatives.

Regarding OmpT protease derivatives, Applicants respectfully submit that OmpT protease derivatives are disclosed in Vandeputte-Rutten *et al.* (2001) "Crystal structure of the outer membrane protease OmpT from Escherichia coli suggests a novel catalytic site." The EMBO Journal 20(18): 5033-5039 (attached herein as **Exhibit 4**), which describes the active site of OmpT protease in detail. Id. at Figures 5 and 7. Additionally, Kramer *et al.* (2001) "Identification of essential acidic residues of outer membrane protease OmpT supports a novel active site." FEBS Letters 505: 426-430 (attached herein as **Exhibit 5**) which describes the effects of site-directed mutagenesis on OmpT protease. Id. at Figure 2.

Taken together, these references discuss the X-ray diffraction analysis of crystal structure of OmpT protease, sequence comparison among Omptin family, mutation analysis in active site of OmpT protease, the total structure of OmpT protease, and the active domain of OmpT protease. Furthermore, these references not only disclose X-ray crystal structure, but also teach how to synthesize various variant or mutant proteins of OmpT protease and how to assay their activity using a synthetic substrate. For example, Vandeputte-Rutten *et al.* it was revealed that all amino acid residues located in the catalytic site, deduced from X-ray crystal structure analysis, were conserved within the whole of the Omptin family. Id. at Figure 6. Moreover, in the reference Kramer *et al.*, several variants were prepared by substituting a highly conserved acidic amino acid for alanine, and their enzymatic activities were determined using a synthetic substrate. Id. at Figure 2. Therefore, taking into consideration the teachings from these prior references, those skilled in the art could prepare and obtain derivatives of OmpT protease which can be used in the claimed invention being provided with the structural (sequence) and functional (assays) parameters of OmpT protease and derivatives thereof.

The specification provides further support for derivatives of ghrelin, Kex2 protease or OmpT protease. For example, on page 57, lines 20 to page 58, line 6, the specification teaches

that ghrelin derivatives can be prepared according to the method described in WO 01/07475 or WO 00/52193.

With respect to Kex2 protease and derivatives thereof used in the claimed invention, on page 58, lines 13-16 of the description of the original English text, teaches that, "Examples of the Kex2 protease derivative include those described in JP-A No. 10-229884, and enzymes belonging to a Kex2 family, representatives of which are Furin and PC1/3." Furthermore, in Examples 7, 13, and 16 of the claimed invention, Kex2 protease is used in the production of ghrelin derivatives.

Regarding to OmpT protease and derivatives thereof, there is a disclosure on page 56, lines 20-24 of the original English text, *i.e.* an *Escherichia coli* OmpT protease (Sugimura & Nishihara (1988) J. Bacteriol. 170: 5625-5632). Furthermore, at page 58, lines 6-13 of the specification teaches that, "[t]he derivative of an OmpT protease or a Kex2 protease is not particularly limited as far as it has the same activity as that of an OmpT protease or a Kex2 protease. Examples of the OmpT protease derivatives include enzymes belonging to an Omptin family, representatives of which are an OmpP protease of *Escherichia coli*, and a pgtE protease of Salmonella, and partial peptides containing an active part of an OmpT protease." Moreover, in Examples 3 and 16, OmpT protease is used for the production of ghrelin derivatives.

In light of the above discussion, Applicants respectfully submit that the specification taken in context with the art provides ample guidance to practice the claimed invention of solid-phase chemical synthesis of a peptide main chain sequence of a peptide fragment on weak acid-cleavable resin and protecting one or more reactive functional groups in a side chain of the peptide. Therefore, Applicants respectfully submit that the specification sufficiently discloses derivatives of ghrelin, Kex2 protease and OmpT protease and, in combination with the art, is sufficient to enable those skilled in the art to carry out the claimed invention without undue experimentation.

The Office Action also asserts that there are, "many different peptides and/or proteins that are substantially similar to ghrelin, OmpT protease, and Kex2 protease may or may not have biological activity." See Office Action at 4. Furthermore, the Office Action states, "The state of the prior art is that even proteins that are 99.99% similar to the wild-type protein are at times not fully active." Specification at 4-5.

Applicants respectfully submit that the Office Action does not provide any support through evidence or references to support these assertions. Applicants note that the analysis and conclusion of a lack of enablement should focus on those factors, reasons, and evidence that lead the Examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. The M.P.E.P. states that this it is important that the USPTO should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. M.P.E.P. § 2164.06(a). While the USPTO does not require references, specific technical reasons are always required. In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

In conclusion, Applicants respectfully submit that the Office Action's assertions that the specification lacks are an improper basis for rejection of the claims under 35 U.S.C. § 112 ¶ 1. Applicants submit that a person of ordinary skill in the art has sufficient guidance from the specification to practice the claimed invention without undue experimentation.

Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing Amendment and Reply, Applicants respectfully submits that claims 24-51 are in condition for allowance, and such disposition is earnestly solicited. Should the Examiner believe that any issues remain after consideration of this Response, the Examiner is invited to contact the Applicants' undersigned representative to discuss and resolve such issues.

Applicants enclose a check in the amount of $1,020.00 to cover the three month extension of time fee. In the event that a variance exists between the amount tendered and that deemed necessary by the U.S. Patent and Trademark Office to enter and consider this Response or to maintain the present application pending, please credit or charge such variance to the undersigned's **Deposit Account No. 50-0206**.

Respectfully submitted,

HUNTON & WILLIAMS LLP

Dated: June 20, 2006 By: _____

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